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Thyrotoxicosis after iodine fortification. A 21 year Danish population based study

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Abstract/Summary

Objective: Monitoring the influence of cautious iodine fortification (IF) on the incidence rate of overt thyrotoxicosis in Denmark with formerly frequent multinodular toxic goitre.

Design: A 21 year (1997-2017) prospective population-based study identified all new cases of overt biochemical thyrotoxicosis in two open cohorts: a Western cohort with moderate iodine deficiency (ID) and an Eastern cohort with mild ID (total n=533,969 by January 1st, 1997). A diagnostic algorithm was applied to all thyroid function tests performed within the study areas. Mandatory IF of salt was initiated in mid-2000 (13 p.p.m.). The present study is a part of DanThyr.

Results: The standardized incidence rate (SIR) of thyrotoxicosis at baseline (1997-1998) was 128.5/100.000/year in the cohort with moderate ID and 80.1 in the cohort with mild ID. SIR increased markedly in both cohorts during the initial years of IF (moderate/mild ID: +39/+52% in 2000-01/2004-05) and subsequently decreased to baseline level (mild ID) or below (moderate ID) by

2008. The decline was due to a marked decrease in the incidence rate among elderly subjects and a moderate decrease among the middle aged. The follow-up period for the mildly iodine deficient cohort was restricted to 2008. A continuous decline in SIR was observed for the remainder of the study period in the area with moderate ID (33% below baseline in 2016-17).

Conclusion: The rise in thyrotoxicosis incidence with cautious mandatory IF returned to baseline level after 7-8 years and levelled out at 33% below baseline in the population with previously moderate ID after 16-17 years.

Introduction

The majority of the world's population lives in iodine deficient areas and iodine fortification (IF) programs cover more than half of the world's population to combat iodine deficiency disorders (IDD)[1]. The World Health Organization (WHO) recommends a urinary iodine excretion of 100-200 µg per day for males and non-pregnant females over the age of 12 years[1].

Long-standing mild and moderate iodine deficiency (ID) increases the risk of developing autonomously functioning nodules in the thyroid gland especially among the middle-aged and elderly[2,3]. An increase in iodine intake may lead to the development of iodine induced hyperthyroidism (IIH), and increased incidence rates of thyrotoxicosis have followed IF programs[4-5].

Denmark was an ID area until 1998[6] with moderate ID in the Western and mild ID in the Eastern parts. This difference was due to different iodine content of tap water[7] and related to regional differences in the occurrence of multinodular toxic goitre that was most frequent in the Western part of Denmark[8]. The frequent toxic and non-toxic goitre and a rise in TSH during pregnancy[9] suggested that the population was iodine deficient. This formed the background for an IF program in Denmark.

The IF of salt in Denmark was accompanied by a program to monitor iodine intake and the occurrence of thyroid disease in two sub-populations with different average iodine intake

(DanThyr)[10]. IF of salt aimed at increasing the daily intake of iodine by an average of 50 µg. This was done cautiously by voluntary iodization of salt in 1998 at a level of 8 p.p.m. This proved to be insufficient and iodization of bread and household salt in Demark was made mandatory by the year 2000 at the level of 13 p.p.m.[11,12].

The short term effects of the Danish IF on the incidence of thyrotoxicosis have been published previously[13]. However, the long term consequences remain to be elucidated. This led us to perform a 21 year follow-up on the incidence of thyrotoxicosis in the area with previous moderate ID and an 11 year follow-up in the area with previous mild ID. The present study was part of the Danish Investigation on Iodine Intake and Thyroid Disease (DanThyr).

Materials and Methods

Population cohort

Prior to initiation of the Danish IF program, two open cohorts were selected for the continuous registration of new cases of thyrotoxicosis. The western cohort comprised inhabitants in Aalborg and the surrounding municipalities in Northern Jutland. By January 1st, 1997 the area encompassed a total of 309,434 inhabitants. The area was moderately iodine deficient with a median urinary iodine concentration (UIC) of 45 µg/l among subjects not taking iodine containing supplements (53 µg/l if all subjects were included) [14]. The Eastern cohort comprised a part of Copenhagen surrounding Bispebjerg Hospital. By January 1st, 1997 this area counted 224,535 subjects and had mild ID with a median UIC at 61 µg/l among subjects not taking iodine containing supplements (68 µg/l if all subjects were included) [14]. Detailed information on the cohort populations was obtained yearly from The Danish Bank of Statistics[15].

The iodine status in the study areas changed during the study period. As part of the DanThyr study three cross sectional studies were performed in the two cohort areas in parallel with the present study. The 1st cross sectional study took place at baseline (1997-98) before IF, the 2nd study in 2004-05 and the 3rd study in 2008-10. Median UIC in the Western and Eastern cohort were

determined at each study respectively (1st: 45 vs 61 µg/l, 2nd: 86 vs 99 µg/l[16], 3rd: 73 vs 76 µg/l[17]). Thus a small decrease in iodine level was observed during late mandatory IF. This decrease was likely caused by a diminished iodine intake from dairy products[18].

The boundaries of the Danish municipalities were restructured by January 1st, 2007 due to a national structural reform. Therefore, the size of the cohort in the area with moderate ID became slightly smaller (n=261,569), but remained unaltered in the mild ID cohort.

Identification of new cases of thyrotoxicosis

The process of identification and verification of incident thyrotoxic patients has been extensively described previously as a part of the DanThyr study[19]. *In short*, a single laboratory at Aalborg University Hospital handled all thyroid function tests from the Western cohort, while three laboratories handled those of the Eastern cohort. All general practitioners, hospital departments and specialist with private practice have unique referral identification numbers for laboratory services. All citizens in Denmark have a unique identification number in the Centralized Person Register (CPR). The CPR numbers and the unique referral identification numbers made it possible to identify new cases of thyrotoxicosis within the selected area by monitoring blood test results for thyroid function as follows: All laboratory tests for serum thyroid stimulating hormone (TSH), triiodothyronine (T_3) and estimates of thyroxine (T_4) sampled within the cohort areas were recorded in a specially designed register database [19]. Potential new cases of overt thyrotoxicosis were identified by a low serum TSH (<0.2mU/l) combined with an elevated serum T_3 and/or T_4. Specific reference ranges were utilized for the evaluation of elevated T_3 and T_4 according to the standards of each laboratory as described previously[19]. Cases previously recorded and verified in the database as either hyper- or hypothyroid were marked as known. Each potential new case was then scrutinized individually by contacting the requesting physician or through available hospital records. From October 2008 and onward, verified data on thyrotoxicosis incidence was available within the Western cohort only.

Statistical methods

Changes over time in sex and age composition of the cohort were adjusted by using the method of direct standardization. Thus the standardized incidence rate (SIR) was calculated[20]. The Danish population as of January 1st, 2005 was used as the standard population. Comparisons to the baseline SIR were made possible by calculating the 95% confidence intervals (95% CI) of the standardized incidence rate ratio (SIRR)[20]. The result was considered significant if the 95% CI of the SIRR did not include 1. Significance level was set at 5 %. Software used for the statistical analysis was: SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. Released 2016.

Results

Changes over time and regional differences

Figure 1 illustrates the SIR of thyrotoxicosis for each of the two cohorts over the course of the three phases of IF: 1st phase, 1997-mid 1998 with no IF; 2nd phase, mid 1998 through mid 2000 with voluntary IF; 3rd phase, mid 2000 through 2017 with mandatory IF. Both populations exhibited an increase in SIR following IF but with distinct geographical differences. The Western cohort with previously moderate ID experienced an early increase of 39% (SIRR (95% CI) = 1.39 (1.24-1.55)) that peaked in 2000-01. The ensuing decline in SIR levelled off and stabilized from 2010 at around one third below baseline (2016-17, SIRR = 0.67 (0.58-0.76)). The Eastern cohort with previously mild ID experienced limited dynamics in thyrotoxicosis in the 2nd phase and early in the 3rd phase after initiation of IF. Subsequent SIR-dynamics showed first a gradual increase that peaked at 52% above baseline in 2004-05 (SIRR = 1.52 (1.31-1.76)) and then a decline to a level that by 2008 was no longer statistically significantly different from baseline (SIRR = 1.12 (0.90-1.38)).

Interestingly, the initially marked difference in the incidence rate of thyrotoxicosis between the two cohorts (SIRR = 1.60 (1.37-1.87) had disappeared by the years 2006-07 (SIRR = 1.08 (0.96-1.23).

Thyrotoxicosis by gender

The incidence of thyrotoxicosis was three to four times higher among women compared to men throughout the entire study period and in both study areas (figure 2). Gender specific incidence rates were 167.8 per 100,000 person years for women and 44.1 for men prior to IF (1997-mid 98) in data pooled from both cohorts. The female preponderance (female/male ratio = 3.80) was largely unaltered throughout the study period that demonstrated parallel dynamics in SIR of thyrotoxicosis in men and women.

Age related differences

The age specific incidence rates of thyrotoxicosis among the three age groups, young (20-39 years), middle aged (40-59 years) and elderly (60+ years), are shown in figure 3. The incidence rates of thyrotoxicosis were strongly correlated with age in both cohorts. At baseline, the SIR of thyrotoxicosis in subjects age 20-39, 40-59 and 60+ years were 49.3, 141.4 and 359.0 per 100,000 person years respectively in the moderate ID cohort and 40.8, 100.1 and 192.4 per 100,000 person years in the mild ID cohort.

In moderate ID, the SIR of thyrotoxicosis increased significantly in all three age groups following IF and peaked around the years 2000-03 (figure 3, upper panel). After an initial increase the SIR declined for the remainder of the study period in the middle aged and elderly, while the incidence rates remained slightly elevated among the young.

The incidence rates peaked earlier in the moderate ID cohort than in the mild ID cohort. Also, a higher relative increase was observed among the young and middle aged (SIRR to baseline, young, 2.22 (1.69-2.92); middle aged, 1.49 (1.24-1.78) in 2002-03) compared to that seen in the elderly (SIRR 1.32 (1.14-1.52) in 2000-01).

In the mild ID cohort, SIR values peaked in 2004-2005 with an age pattern in SIRR similar to that of the moderate ID cohort (SIRR to baseline, young, 2.50 (1.85-3.38); middle aged, 1.43 (1.08-1.90); elderly, 1.34 (1.08-1.65) as shown in figure 3, lower panel.

The incidence of thyrotoxicosis was higher only in the younger age group by the end of the period studied (SIRR among young, moderate ID: 2.16 (1.59-2.95) in 2016-17; mild ID: 2.08 (1.35-3.20) in 2008). In fact, the incidence of thyrotoxicosis was lower among the middle aged in the area of moderate ID (SIRR to baseline, middle aged, 0.68 (0.53-0.87); elderly, 0.39 (0.32-0.48)) by the end of the study in 2016-17. The difference in incidence rates between the three age groups had disappeared by the end of the study in the moderate ID cohort. The incidence rates in the mild ID cohort were at baseline level by 2008 (SIRR, middle aged, 1.04 (0.69-1.54); elderly, 0.88 (0.65-1.20)). No meaningful analysis could be performed in the young age group as the number of new cases per year was very low.

A noticeable shift in age specific incidence rates was seen in the moderate ID cohort. The incidence rate of thyrotoxicosis increased with age prior to IF, while this was no longer the case at the end of the study period. Thus, the incidence rate was constant from the age of 30 and up by 2016-17 (figure 4).

Discussion

Principal Observations

This prospective cohort study on long term thyrotoxicosis incidence after iodine fortification demonstrated a two phase course with time line, gender and age details. An immediate increase in the incidence of thyrotoxicosis in moderate ID areas was followed by a marked decline that levelled out at 33% below baseline at around the year 2010. Changes were parallel among men and women but with distinct age differences. The increase in incidence rate was relatively highest among the young, while the decline was most pronounced among the elderly. The temporary increase in

thyrotoxicosis incidence seen in the mild ID area after mandatory IF reverted back to baseline level by 2008. The study period in the area with mild ID ended by 2008, which is a likely cause for not seeing a decline below baseline.

Comparison with other studies

The DanThyr study includes cross sectional studies performed in the same two regions of Denmark as the present study. The prevalence of subclinical thyrotoxicosis decreased and there was a tendency towards decreased prevalence of overt thyrotoxicosis from the first (1997-98, n=4649) to the second cross sectional study (2004-05, n=3570)[21]. The prevalence of undiagnosed overt hyperthyroidism was reduced by 61.0 % in the moderate ID cohort and by 50.8 % in the mild ID cohort (non-significant). The numbers for subclinical hyperthyroidism was reduced by 55.2 % and 59.4 % ($p < 0.01$).

Our finding of an increased incidence rate in the years following IF is in accordance with a number of studies of different design and follow-up[4,22,23,24,25,26]. Iodine induced hyperthyroidism (IIH) was documented in Tasmania based on hospital referrals back in 1966[4,27]. The incidence rate of thyrotoxicosis rose from 24/100,000 prior to IF reaching a maximum of 125/100,000 in 1967, with a slow decline over the next decade. The rise occurred after IF of bread salt and the introduction of iodophores in the dairy industry around 1966[4,27]. Similarly, an increase in the iodine content of salt in Switzerland from 7.5 to 15 p.p.m. in 1980 was followed by an early increased incidence rate of thyrotoxicosis in the first year of 27% as estimated from the number of hospital referrals[24]. By 1988/1989 the incidence rate had declined and was 56% below baseline value[24]. The decrease was due to a markedly lower occurrence of multi-nodular toxic goitre and to a lesser extent a decline in the number of cases of Graves' disease[24]. This is in accordance with our findings of the most marked decline in incidence rate in elderly subjects, among whom multinodular toxic goitre is the leading cause of thyrotoxicosis[8]. Likewise, IF of salt in Austria was increased from 7.5 to 15 ppm. in 1990. This was followed by a substantial increase in the occurrence of both multinodular toxic goitre and Graves' disease. The incidence rate of multinodular toxic goitre was almost at the baseline level 5

years later, whereas the incidence rate of Graves' disease (GD) remained elevated throughout the study period[22]. Similarly, we found a major increase in the incidence rate of thyrotoxicosis following IF among young subjects (20-39 years), and it could be speculated that this increase was caused by GD, which is the most common cause of hyperthyroidism among the young[8]. Interestingly, the initial increase in incidence of GD was not followed by an increased occurrence of Graves' orbitopathy[28].

Monitoring of the use of anti-thyroid medication in Denmark was included in the DanThyr studies[29]. A gradual rise in the amount of anti-thyroid medication sold in the area of moderate ID was manifest at 46% above baseline level in 2001. This is consistent with our finding of a 39 % increase in incidence of thyrotoxicosis in 2000-01. A subsequent decline in the sale of anti-thyroid medication reached pre-fortification level in the year 2005 for the Western part of Denmark[29]. This was parallel to the development in incidence rate of thyrotoxicosis demonstrated in the western cohort. The marked increase in thyrotoxicosis incidence rate in 2004-05 in the Eastern cohort in the present study did not see a clear-cut parallel in the use of anti-thyroid medication in Eastern Denmark[29]. This cannot be explained by a more frequent use of radio-iodide treatment[30]. The absence of increased use of anti-thyroid medication in Eastern Denmark despite the increased incidence of overt thyrotoxicosis may be explained by a higher frequency of mild cases left untreated, more cases of transient thyrotoxicosis or increased use of surgical treatment.

Possible mechanisms involved

IIH may be caused by more than one mechanism. Among the elderly with longstanding nodular goitre due to ID, an increase in iodine intake may trigger hyperfunction of the pre-existing nodules due to a combination of autonomy and increased substrate availability[31,32].

The marked drop in incidence rate of thyrotoxicosis among the middle-aged and elderly could be caused by the lower tendency for developing autonomously functioning nodules. This is further supported by cross sectional ultrasonographic studies of thyroid nodules within the two cohort areas before (1997-98) and long after (2008) IF. A markedly decreased prevalence of thyroid nodules was

observed when adjusted for age, especially in the moderate ID area, as well as a tendency for diminishment and disappearance of existing nodules[33].

A higher degree of thyroid autoimmunity is also likely to be involved. It may be speculated that the surge in IIH among younger subjects was caused by GD as autonomously functioning nodules are rare in this age group[8]. Increased prevalence of thyroid autoantibodies has been found among especially the young after IF, which supports the notion that increased thyroid autoimmunity may explain the IIH observed among this age group[34].

Implications for IF programs

Our results support a cautious approach to IF in a population with mild to moderate ID. Increasing the average iodine intake cautiously by around 50 μg per day successfully reduced the incidence rate of thyrotoxicosis by more than 33 % in a moderately iodine deficient population within two decades. It seems credible to expect a decline in incidence rate of thyrotoxicosis below baseline level in the mildly iodine deficient areas as well. This was not seen in our study, probably due to the much shorter study period in the mild ID cohort. Some degree of IIH seems unavoidable but the excess number of thyrotoxicosis patients during the IIH surge was more than compensated by the fewer cases in the immediately succeeding years. After introduction of IF special attention should be given to the young who experience a relatively higher level of IIH and the least subsequent decline in incidence rate.

Strengths and limitations

Previous studies of the influence of IF on the risk of thyrotoxicosis were mainly based on patients referred to hospital settings[4,22,35]. The present study included both patients referred to hospital and those managed solely in primary care, and thus avoids the selection bias seen in studies based on hospital referral[35]. Furthermore, the long follow-up period and the inclusion of a baseline period prior to IF make the present study distinctive among systematic epidemiological surveys of the incidence rate of thyrotoxicosis after IF.

The registration of incident thyrotoxicosis cases in the mild ID cohort ceased in 2008 due to limited staff availability. Whether a decline or an unaltered incidence of thyrotoxicosis would have occurred in this area remains unsettled. However, it does not change the overall conception that IF has proved to be effective in order to lower the burden of thyrotoxicosis in Denmark. Yet, the distribution of the nosological subtypes of thyrotoxicosis and possible change due to IF remains to be elucidated.

Treatment of subclinical thyrotoxicosis may have occurred more frequently in the later years of the present study, which could lead to subjects evading our algorithm, as they may never become overtly thyrotoxic. However, the decline in use of anti-thyroid medication on a national scale suggests otherwise as an increase in use of anti-thyroid medication was to be expected if more patients were treated for subclinical thyrotoxicosis[29]. Furthermore, the diagnostic and therapeutic blood sampling activity more than doubled during the course of the study period (data not shown). This could diminish the pool of undiagnosed overtly thyrotoxic subjects, hence increasing rather than decreasing the incidence rates in the present study due to more focus on thyroid disease.

Conclusion

Mandatory iodine fortification successfully reduced the incidence rate of thyrotoxicosis in Denmark by 33% in a moderately iodine deficient population. The decline in incidence rate was conspicuous for the elderly suggesting that higher iodine intake may partly prevent the development of multinodular toxic goitre. Similar changes may have occurred in the areas of mild ID, although the shortened study period prevented us from verifying this. Further studies should focus on clarifying the nosological subtypes of thyrotoxicosis.

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Legends to figures

Figure 1: Age standardized incidence rates of thyrotoxicosis per 100,000 person years (pyar) in the two cohorts from 1997-2017.

Voluntary iodine fortification (IF): initiated in July 1998 with 8 ppm iodine in table salt and salt used by the food industry.

Mandatory IF: initiated in July 2000 with 13 ppm iodine in all table salt and salt used for the production of bread.

The error bars indicate the 95 % confidence intervals (CI) for the incidence rates. An asterix * indicates a statistically significant difference compared to baseline (1997-mid 1998, before IF), with a 95% CI for SIRR that does not include 1. Solid line: Western cohort in and around Aalborg City with moderate iodine deficiency (45µg/l) prior to IF. Dotted line: Eastern cohort in Copenhagen with mild iodine deficiency (61 µg/l) prior to IF. The study period for the cohort with mild iodine deficiency was not possible beyond 2008.

Figure 2: Gender specific incidence rates with 95% CI of thyrotoxicosis per 100,000 person years (pyar) in the moderately and mildly iodine deficient cohorts from 1997-2017. Error bars represent 95% CI. Data were age standardized.

An asterix * indicates a statistically significant difference compared to baseline (1997-mid 1998, before IF), with a 95% CI for SIRR that does not include 1. M = Males. F = Females.

Figure 3 a-b: Age specific incidence rates of thyrotoxicosis per 100,000 person years (pyar) with 95% CI. Subjects have been split into three age groups: 20-39, 40-59 and 60+ years. Upper panel (a) shows data from the cohort with moderate iodine deficiency from 1997-2017. Lower panel (b) shows data from the cohort with mild iodine deficiency from 1997-2008.

Figure 4: Age specific incidence rates of thyrotoxicosis per 100,000 person years (pyar) with 95% CI from 1997-mid 1998 (prior to IF) and 2016-2017 (late mandatory IF) in the Western cohort with moderate ID prior to IF.

Figure 1

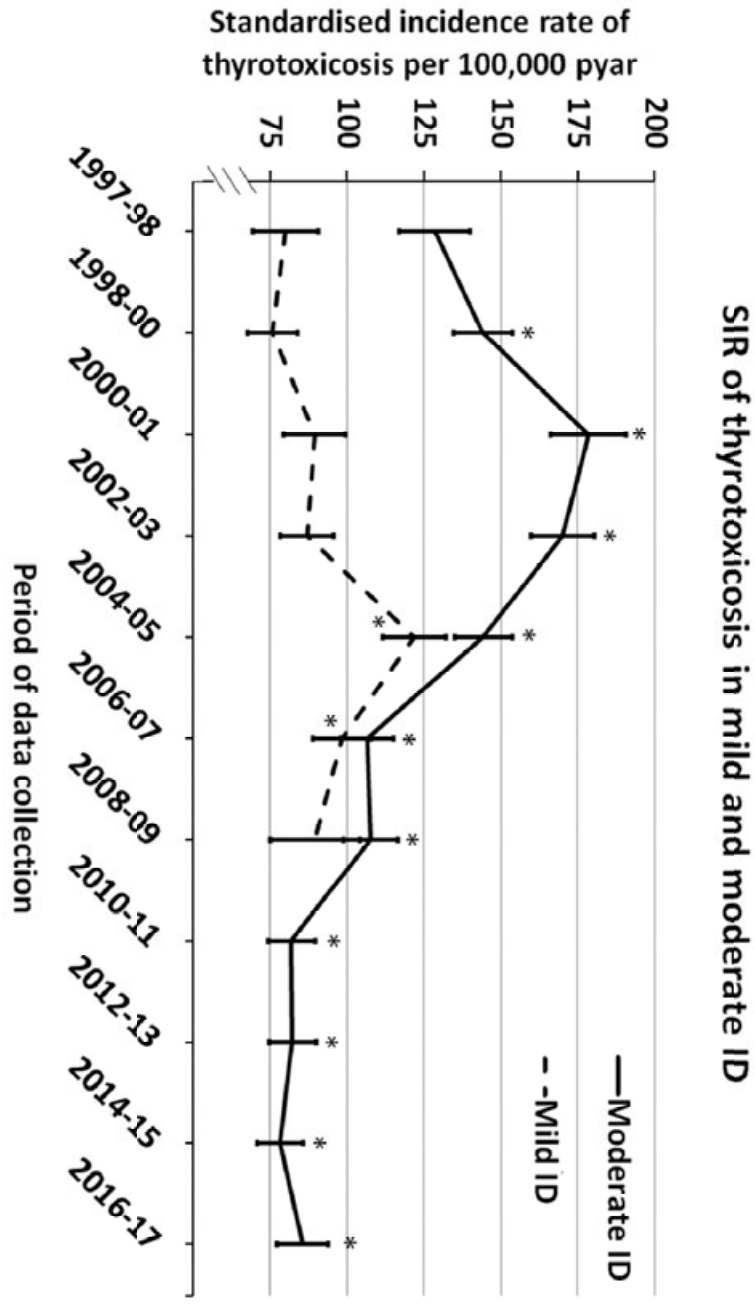

Figure 2

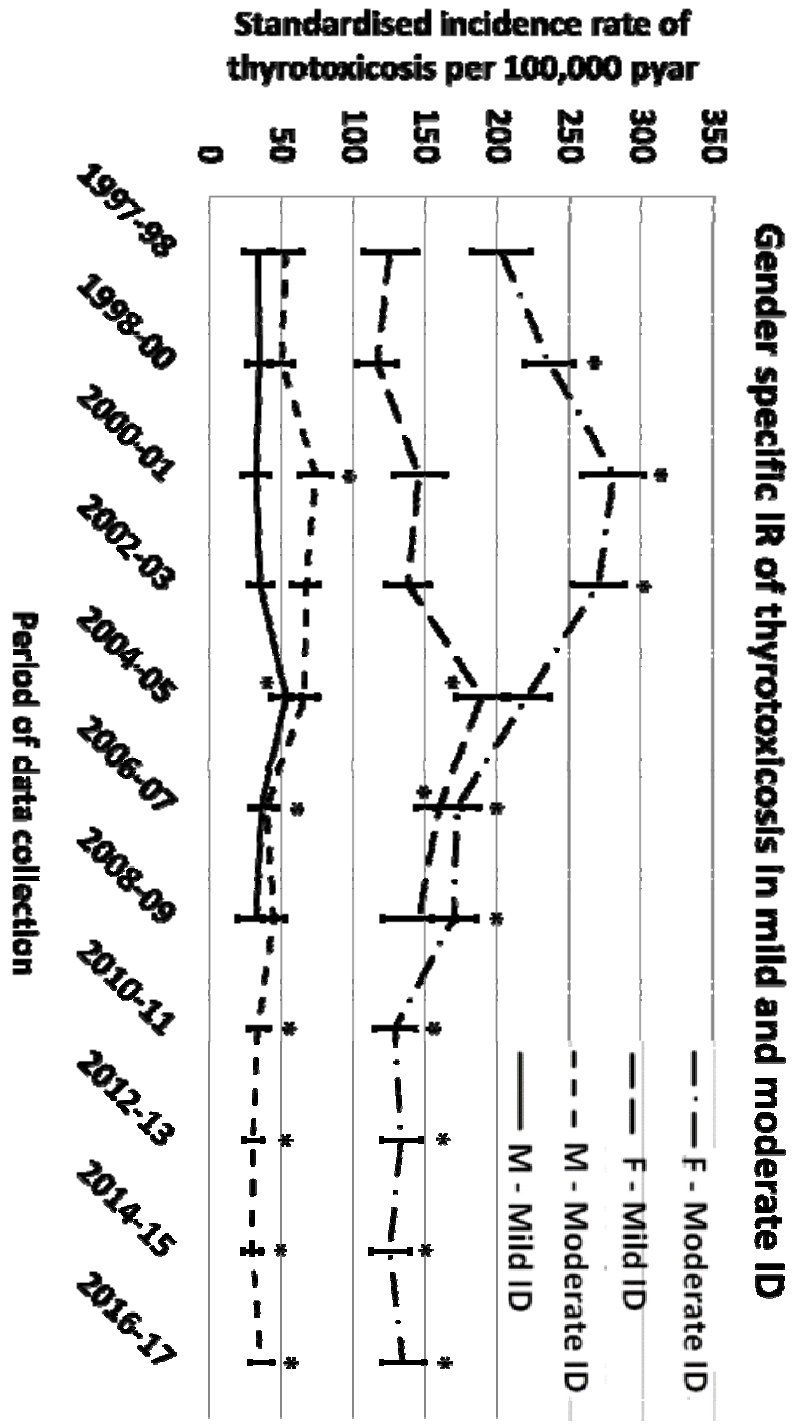

Figure 3

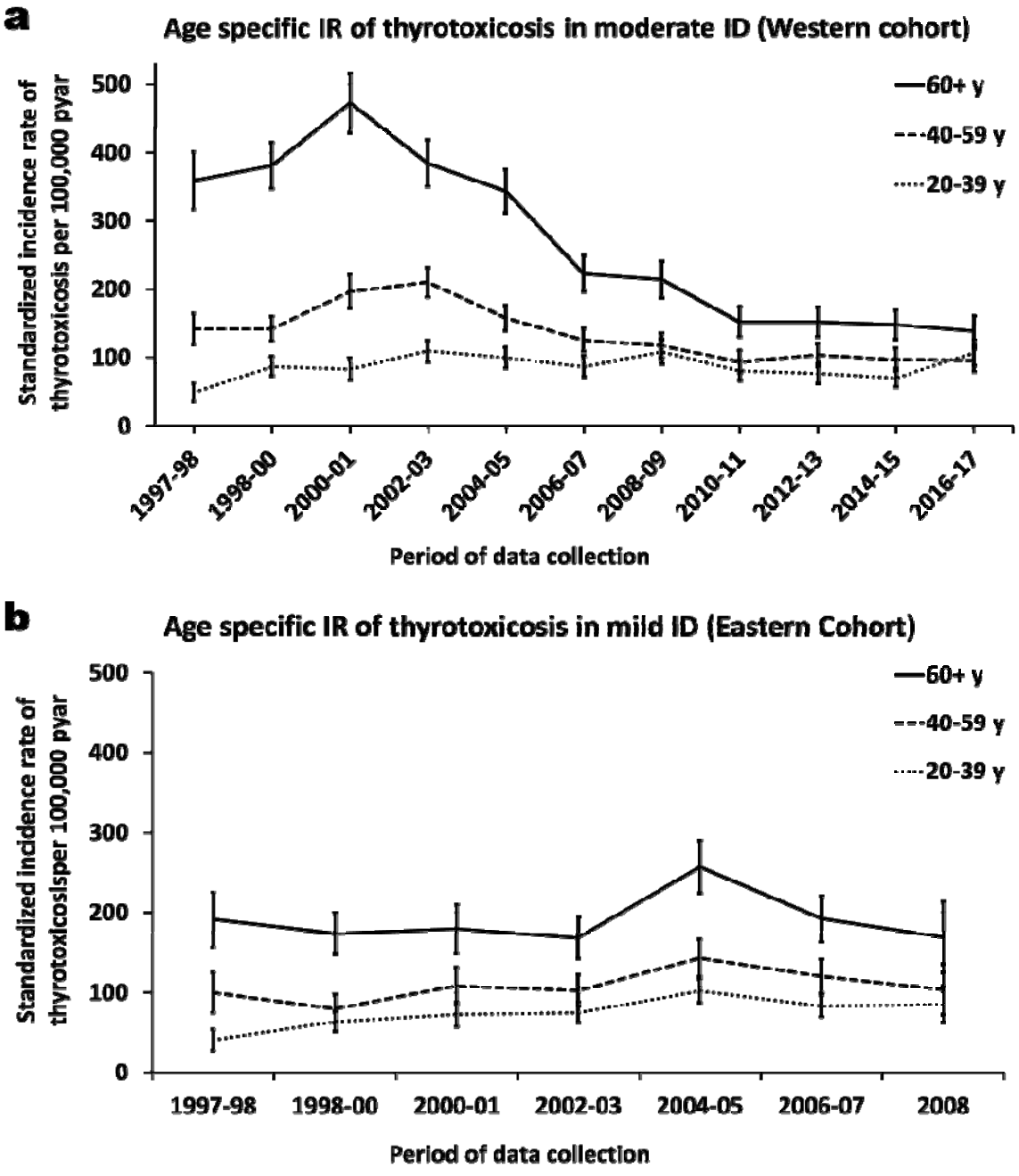

Figure 4